

Appl. No. 09/888,320  
Amdt. dated 02/11/2004  
Amendment under 37 CFR 1.116 Expedited Procedure  
Examining Group

PATENT

47. (Previously presented) A kit of claim 46, further comprising a mutated EtaA gene for use as a positive control.

48. (Currently amended) A kit of claim 47, wherein said mutated EtaA gene is selected from the group consisting of (a) a mutated EtaA gene comprising a frameshift mutation selected from the group consisting of a deletion at position 65, an addition at position 567, and an addition at position 811, and (b) a mutated EtaA gene comprising a single nucleotide polymorphism which causes an amino acid substitution selected from the group consisting of: G43C, P51L, D58A, Y84D, T186K, T342K, and A381P.

### REMARKS/ARGUMENTS

#### **I. Status of the Claims**

Claims 1-5, 8-12, 21, 22, 25, 28, 29 and 34-48 are pending. Claims 6, 7, 16, 23, 24, 26, and 27 have been previously cancelled, claims 13-15, 17-20, and 30-33 have been withdrawn as drawn to non-elected inventions, and claims 34-48 were previously added.

#### **II. The Present Amendments**

The present amendments add no new matter.

The amendments to claim 1 recite that the claimed method is a method of determining the ability of a *Mycobacterium tuberculosis* (Mtb) bacterium to oxidize ethionamide, thiacetazone, or thiocarlide by detecting an amino acid in an EtaA gene which differs from that of SEQ ID NO:2 by comprising any of 10 different mutations. The recitation regarding the ability of Mtb to oxidize ethionamide, thiacetazone, or thiocarlide is supported throughout the specification, including claim 16 as originally filed. The specific mutations in SEQ ID NO:2 are likewise supported throughout the specification, including claims 2 and 4 as originally filed.

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The recitation of claim 21 has been amended to recite that the Mtb are resistant to treatment with ethionamide, thiacetazone, or thiocarlide. The recitation is supported throughout the specification, including page 8, paragraph 23. The claim also now recites that the mutation in the EtaA gene is selected from a group of mutations recited in the claim. The mutations recited are supported throughout the specification, including Figure 4, panels B and C.

Claim 25 has been amended in the same manner as claim 1. The amendments to claim 25 are supported by the passages noted in connection with claim 1.

Claim 34 has been amended to recite methods in which the amino acid sequence of the EtaA gene in an Mtb organism is selected from a group of mutations recited in the claim. The mutations recited are supported throughout the specification, including Figure 4, panels B and C.

The dependency of claim 37 has been changed to reflect the cancellation of claim 36.

Claim 44 has been amended to recite methods in which the amino acid sequence of the EtaA gene in an Mtb organism is selected from a group of mutations recited in the claim. The mutations recited are supported throughout the specification, including Figure 4, panels B and C.

Applicants respectfully submit that entry of the amendments is appropriate at this time as they place the claims in condition for allowance or, alternatively, place them in better condition for appeal.

### **III. The Office Action**

The Action rejects the pending claims on several grounds. Applicants amend in part and traverse. For the Examiner's convenience, the rejections are discussed below in the order in which they are presented in the Action.

#### **A. Rejection of the claims under §112, first paragraph**

Claims 1-5, 8-12, 16, 21, 22, 25, 28, and 29 are rejected under 35 U.S.C. § 112, first paragraph, as not enabled. The Action concedes that the specification is enabled for

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methods of determining the ability of a *Mycobacterium tuberculosis* ("Mtb") bacterium to oxidize a thiocarbonyl or thioamide found in the drugs ethionamide ("ETA"), thiacetazone ("TA") or thiocarlide ("TC") by detecting one of the mutations exemplified in the specification in the Mtb EtaA gene. The Action contends, however, that the specification does not provide enablement for methods of determining the ability of an Mtb to oxidize any thioamide or any thiocarbonyl by detecting any mutation in the EtaA gene of an Mtb.

In this regard, the Action contains a litany of what it asserts are omissions in the specification. For the sake of good order, the Applicants will respond briefly to each

(1) The specification "omits a teaching of a mutation in every nucleic acid of the EtaA gene that is associated with resistance to all of the drugs in both of the claimed drug classes." Action, at page 5.

Applicants assume that what the Action refers to as "every nucleic acid of the EtaA gene" refers to mutations in the sequence of the wild-type gene, SEQ ID NO:1. Applicants respectfully note that the claims as presented following the last amendment recite mutations in the gene which encode an amino acid sequence which differs from the wild-type amino acid sequence, as set forth in SEQ ID NO:2. It is part of the teaching in the art that Mtb has a low rate of synonymous mutation and that the Sreevatsan et al. study showed that 95% of mutations in Mtb genes were found to be associated with amino acid replacements. Thus, the art of record teaches that there is a high expectation that any mutation in the EtaA gene would result in an amino acid change.

Applicants also respectfully note that one of the reasons the specification warranted publication in PNAS (as previously noted, the specification was the basis for DeBarber et al., PNAS 97(17):9677-6682 (2000)) was that all but one Mtb isolate from patients resistant to ETA with mutations in EtaA were also resistant to thiocarlide, even though the patients had never been treated with this drug. There is therefore also a very high expectation that any particular amino acid change would be associated with resistance to all the drugs in the claimed classes.

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(2) The specification "does not teach the way in which each drug . . . differs; nor does it teach the characteristic shared between all drugs responsible for conferring the antibiotic resistance." Action, at page 5.

Applicants observe that the specification indicates that it appears that ETA acts through EtaA-catalyzed S-oxidation (specification, at page 26, lines 14-16 and page 27, lines 20-24), and indicates that "EtaA is directly responsible for thioamide S-oxide oxidative activation." Specification, page 27, lines 20-24. Thus, the specification does provide a characteristic shared by the claimed classes of drugs. Applicants respectfully note that ethionamide, thiacetazone and thiocarlide are all thiocarbonyl drugs, that is, drugs that contain a sulfur double-bonded to a carbon. Applicants note that ethionamide and thiacetazone are also thioamides, since the carbon that is double bonded to the sulfur is also bonded to an NH<sub>2</sub> group. (For the Examiner's convenience, Applicants note that the structure of ETA is shown in the DeBarber PNAS paper of record, on page 9681, as compound 1 of Figure 5, while thiacetazone is shown on page 9680 as compound 11 of Figure 4A.)

Applicants respectfully note that the persons of skill in the art are typically M.D.s and Ph.D.s and can be expected to understand the relationship between thiocarbonyl and thioamide drugs given the specification's teachings about the thioamide S-oxide oxidation activation pathway. Finally, Applicants respectfully note that none of the drugs are "responsible for conferring the antibiotic resistance," and surmise that the Action meant that the specification does not explain why changes in the EtaA gene confer drug resistance. Applicants respectfully maintain that, given the specification's teachings regarding the thioamide S-oxide oxidation activation pathway, persons of skill would assume that changes in the amino acid sequence of the EtaA gene would confer resistance to the drugs by reducing the ability of the organism to catalyze S-oxidation.

(3) "The specification teaches that the drugs, ETA and TA and TC confer different resistance status to the bacterium (Fig 4C). The specification does not teach how or why such supposedly similar thioamide or thiocarbonyl-containing antituberculosis medications confer varying degrees, if at all, of drug resistance." Action, at page 5. The Action cites *In re*

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*Vaech* as requiring that the specification must teach how to make and use the invention as broadly as claimed and *In re Fisher* as requiring more guidance as the art is less predictable.

Applicants respectfully note that the question is whether a particular Mtb isolate from a patient is susceptible to treatment with a thioamide or thiocarbide. None of the drugs are "responsible for conferring [] antibiotic resistance." Applicants surmise that the Action intended to assert was that the specification does not explain why changes in the *EtaA* gene confer drug resistance. Applicants respectfully maintain that, given the specification's teachings regarding the thioamide S-oxide oxidation activation pathway, persons of skill would understand that changes in the amino acid sequence of the *EtaA* gene would confer resistance to the drugs by reducing the ability of the organism to catalyze S-oxidation, as explained in the preceding section. Thus, Applicants maintain that the specification does teach how to make and use the invention as broadly as claimed, and that the invention is not unpredictable. Thus, Applicants maintain that the invention as claimed meets the requirements articulated in *Vaech* and *Fisher*.

(4) "[O]ne cannot readily anticipate which of the mutations within the gene (i.e. mutations other than those set forth in Table 4C) actually result in the inability to oxidize thiocarbonyl groups and that would be associated with a patient that is resistant to such thiocarbonyl-containing antituberculosis medications, as opposed to those frameshifts or polymorphisms that result in drug sensitivity." Action, at page 6. The Action acknowledges the Sreevatsan et al. teachings regarding the low rate of synonymous mutations in Mtb, but alleges that "the reference does not teach a correlation between the occurrence of amino acid change and specific drug resistances." *Id.* The Action further acknowledges that Sreevatsan teaches "a strong suspicion that the variation has functional significance, such as antibiotic resistance," (Action, at page 6, quoting Sreevatsan), but states that "the reference provides no data relating the amino acid changes to any antibiotic resistance." *Id.* Finally, the Action states that "applicants have not shown that every mutation in the *EtaA* gene will reduce the ability of a Mtb organism to oxidize a thioamide or thiocarbonyl drug, and therefore increase resistance of the organism." Action, at pages 6-7, bridging sentence.

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As the Action itself acknowledges, the Sreevatsan reference shows that the art taught, prior to the filing date, that there was a "strong suspicion" that a mutation causing a change in amino acid sequence in Mtb would have "functional significance, such as antibiotic resistance." The Action indicates that this is not sufficient because, it states, the amino acid changes have not been correlated to any antibiotic resistance. Thus, it appears that, to find the claims enabled, the Action would require that the reference have cataloged every mutation of the EtaA gene and its effect on ETA, TA, and TC resistance. Failing that, Applicants presume that the Action would require that the Applicants have mutated each amino acid residue encoded by EtaA and tested the resulting construct for S-oxidation activity. Applicants maintain, however, that the patent laws do not require practitioners to conduct what would be an impossible number of tests. Rather, the standard is whether there is predictability. As noted in the Applicants' last amendment, the Sreevatsan reference sets forth the results of a study of sequence data for 26 genes in hundreds of Mycobacterium isolates. It reports that a "[c]ompilation of the two megabases of sequence data for the 26 genes revealed that greater than 95% of nucleotide substitutions caused amino acid replacements or other mutations in gene regions linked to antibiotic resistance," (page 9870, bottom right), and that "greater than 95% of nucleotide changes were directly associated with antibiotic resistance." (*Id.*, page 9873, left column, second full paragraph, emphasis added.) The authors concluded that "[t]he lack of allelic diversity means that when amino acid polymorphisms, or regulatory region nucleotide variation are observed, there should be strong suspicion that the variation has functional consequences, such as antibiotic resistance." *Id.*, at page 9872, bottom right hand column.

Sreevatsan thus indicates that a mutation in an Mtb gene predictably has "functional significance," and that the functional significance of a mutation of a gene associated with susceptibility to an antibiotic is resistance to that antibiotic. The Sreevatsan reference therefore gives substantial predictability that a mutation that causes an amino acid change in the product of the EtaA gene will cause increased resistance to drugs metabolized by the EtaA gene product.

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The correlation between changes in amino acid sequence and changes in resistance is demonstrated in the specification, which shows the uniform effect of changes in amino acid sequence from the wild type sequence in rendering organisms with the mutations resistant to ETA and TA, and 9 out of 10 of the organisms resistant to TC. Thus, the specification shows there is a very high degree of predictability that changes in the amino acid sequence will result in increased resistance to thioamides and thiocarbonyl drugs.

This predictability is further demonstrated by the post-filing date art. Attached hereto in this regard is a copy of Morlock et al., *Antimicrob. Agents Chemother.* 47(12):3799-3805 (Dec. 2003). This very recent study characterized the DeBarber et al. PNAS article as showing that "ETH [ethionamide] must undergo activation via an EthA-mediated process . . . Genetic alterations leading to reduced EthA activity would be expected to result in increased ETH resistance." Morlock, *supra*, at page 3800, left column. Further, Morlock et al. sequenced 41 Mtb isolates collected from the U.S., Russia, and Brazil. Of these, 15 had mutations in the EtaA gene (Morlock et al. uses the terminology of Baulard et al., *J. Biol. Chem.* 275(36):28326-31 (Sept. 2000), which called the gene "EthA" and ethionamide "ETH"). Morlock, at page 3801, bottom left column. The mutations were all different, and were previously unreported. See, abstract. That is, they are not the same mutations as reported in DeBarber. All of the 15 isolates with mutations in the EtaA gene had minimum inhibitory concentrations (MICs) of 50 µg/ml or higher. Morlock, at page 3802, bottom left column and Table 2. By contrast, no isolate sensitive to ETA had a mutation in the EtaA gene. See, Table 2.

In short, the Applicants showed 9 mutations in EtaA and found increased resistance to ETA, TA, and TC (and, in one case, an isolate which remained susceptible to TC). No mutations were associated with increased sensitivity to these drugs. Morlock et al. found an additional 15 mutations in the EtaA gene, all of which were associated with increased resistance to ETA, the only of the claimed drugs they tested. In full agreement with the expectation set forth in the present specification, no isolates were found which had a mutation in the EtaA gene and which were susceptible to ETA.

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Thus, the expectations stated in the specification have continued to be confirmed and expanded by the art since the filing of the present application. Applicants respectfully maintain that the Action fails to set forth a *prima facie* case that there is any unpredictability that mutations in the *EtaA* gene will not result in increased resistance to ETA or to the other drugs claimed.

(5) "Response to Arguments"

At pages 7 to 10 of the Action, the Action replies to responses made by the Applicants in the previous amendment. For the most part, the Action's replies here echo the assertions already responded to above. For the sake of a complete response, however, Applicants will briefly comment on them.

(a) Comments on Figure 4C of the specification. At page 8 of the Action, the Action explains that the intent of the previous office action was to refer to Strain AS7TAR of Figure 4C of the specification, which shows a *Mtb* isolate with a mutation in the *EtaA* gene that shows susceptibility to treatment with TC. The Action maintains that the existence of this example constitutes a teaching that a mutation in *EtaA* does not confer resistance to all thioamines and thiocarbonyls. Applicants understand that the Action maintains a perfect correlation to support the claim, while Applicants maintain that the results shown demonstrate a high degree of correlation between such mutations and the existence of resistance to the claimed drugs, a correlation which is further supported by the results presented in the post-filing date art cited above. Notwithstanding the foregoing, however, to expedite prosecution, the claims have been amended to recite that the methods pertain to predicting resistance to ethionamide, thiacetazone, and thiocarlide.

(b) Comments on various statements from the previous office action

At pages 8-10, the Action replies to a series of contentions regarding interpretation of the information presented in the specification. The contentions and Applicants' responses, are as follows:



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(i) that Sreevatsan does not correlate amino acid changes and any antibiotic resistance, Action at page 9. This contention has been addressed in Section III A (1), above.

(ii) that Applicants have not shown that every mutation in the EtaA gene will reduce the ability of a Mtb organism to oxidize a thioamide or thiocarbonyl, Action, at page 9. This contention has been addressed in Section III A (4), above.

(iii) that the specification does not teach a common property of the drugs that is responsible for the shared resistant phenotype. Action at page 9. This contention is addressed in Section III A (2), above.

(iv) the "specification should clearly assert the exact mechanism by which each of the claimed drugs metabolize the mutant EtaA gene product and in doing so, asserting the common thread shared by all drug classes. It is presently highly unpredictable to assume that all drugs in both of these claimed classes share the same mechanism." Action, at pages 9-10, bridging sentences. Applicants respectfully note that there is no requirement in the patent statute that an applicant have any understanding of the mechanism by which an invention works. There is certainly no requirement that the applicant "clearly assert the exact mechanism" by which the invention works. The Examiner is respectfully reminded that aspirin was known and used for close to a century before its mechanism of action in repressing prostaglandin synthesis was elucidated. Aspirin was and is, nonetheless, a useful product.

Presumably, the Action's contention is meant to convey that in the context of the present invention, it is unpredictable unless the applicant can explain the mechanism shared by the three drugs noted. Applicants note, however, that the isolates analyzed in Figure 4C of the specification were selected because they were from patients resistant to ETA. All but one of the Mtb organisms from these patients were found to be resistant to TC, even though they had never been challenged with TC. See, page 30, lines 13-16. Thus, Applicants respectfully maintain that the specification shows a high degree of predictability that mutations in EtaA are predictive of increased resistance to thioamide and thiocarlide drugs. Notwithstanding the foregoing, to expedite prosecution, the claims have been amended to recite ETA, TA, and TC:

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6. Application of the rejections to new claims 34-48

Claims 34-48 were added in the Applicants' last amendment, but recite the specific drugs ETA, TA, and TC, rather than thioamide or thiocarbide drugs generally. Pages 10-15 of the Action apply to these claims the same rejections discussed in detail above. Pages 10-15 assert that, while these claims recite specific drugs, the claims are not enabled for any mutation in the EtaA gene. The Action repeats the arguments set forth and responded to above, including the alleged requirement that the specification teach the exact way each drug differs, the exact class in which the three drugs belong, and what structural motif they have that is responsible for this classification. These arguments have been discussed and responded to above.

The Action further states that the specification fails to teach the "common property represented within each mutation that is responsible for the resulting drug resistance," Action, at page 12, and "how or why such supposedly similar thioamide or thiocarbonyl-containing antituberculosis medications confer varying degrees, if at all, of drug resistance," Action, at page 13. Applicants respectfully note that the medications do not confer degrees of drug resistance. As Applicants noted in response to the previous office action, which contained similarly inaccurate wording, they surmise that the Action meant to convey that the specification does not explain how the mutations in the EtaA gene confer differing degrees of drug resistance to the organisms containing the mutated gene.

Applicants respectfully remind the Examiner that there is no requirement in the patent law that applicants for a patent understand or explain the basis for their invention. Presumably, the present Action recites this contention to explain why it considers it unpredictable that the results of the specification could be extended to other mutations in the EtaA gene. But, as the Applicants noted in their last response, the Sreevatsan reference, already of record in this proceeding, sets forth the results of a study of hundreds of Mycobacterium isolates. The Sreevatsan authors reported that a "[c]ompilation of the two megabases of sequence data for the 26 genes revealed that greater than 95% of nucleotide substitutions caused amino acid replacements or other mutations in gene regions linked to antibiotic resistance," (page 9870, bottom right), and that "greater than 95% of nucleotide changes were directly

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associated with antibiotic resistance." (*Id.*, page 9873, left column, second full paragraph.) The authors concluded that "[t]he lack of allelic diversity means that when amino acid polymorphisms, or regulatory region nucleotide variation are observed, there should be strong suspicion that the variation has functional consequences, such as antibiotic resistance." *Id.*, at page 9872, bottom right hand column.

The results in the present specification show that every mutation in the *EtaA* gene was associated with increased resistance to ETA and to TA, and all but one was associated with increased resistance to TC. The recent report by Morlock et al., provided with this Amendment, shows that every isolate studied that had a mutation in *EtaA* had increased resistance to ETA. Accordingly, the results reported by Sreevatsan, by the Applicants, and by Morlock, are consistent and show that there is a high degree of predictability that mutations in the *EtaA* gene cause resistance to ETA, TA, and TC. To expedite prosecution, however, the claims have been amended to recite the particular mutations set forth in the specification.

#### 7. Conclusion

In short, Applicants maintain that the Action has not made out a *prima facie* case of unpredictability. Every single mutation found thus far in *Mtb EtaA*, by Applicants or by other researchers, has been correlated with increased resistance to ETA, and no mutation has been reported that is not associated with increased resistance to ETA. Accordingly, Applicants maintain that it is predictable that mutations in the *EtaA* gene are correlated with resistance to thioamide drugs, and highly correlated with thiocarbonyl drugs in general. Nonetheless, to expedite prosecution, the claims have been amended to recite the mutations set forth in the specification. As amended, the claims are believed to be free of the rejections posed by the Action.

#### B. Rejection of the Claims As Obvious

Claims 25 remains rejected, and claim 46 is newly rejected, under 35 U.S.C. § 103(a) as obvious over an unpublished sequence deposited by Badcock and Churcher (hereafter,

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"Badcock"), in view of Philipp et al., PNAS USA 93:3132-3137 (1996) ("Philipp") and further in view of Ahern, *The Scientist*, 1995 ("Ahern"). Applicants traverse.

As noted in Applicants' last amendment, Badcock is an unpublished sequence of 38230 nucleotides from the genome of Mtb, nucleotides 14983 to 16452 of which are stated encode a probable monooxygenase. Philipp is a report of an integrated map of the Mtb genome. Ahern is simply an article on the advantages of kits. According to the Action, Badcock teaches the EtaA gene of Mtb and its possible function as a monooxygenase. Action, at page 10. Philipp is stated to establish an ordered set of DNA fragments and supposedly, to teach using primers specific to the Mtb sequence of genomic DNA to facilitate gene mapping.

As noted, the rejection under §103(a) relies on combining Badcock, Philipp and Ahern. Applicants pointed out in their last Amendment that a combination of references requires the Action to show some teaching, suggestion, or motivation in the art to combine the references. *See, e.g., In re Geiger*, 815 F.2d 686 (Fed. Cir. 1987). As the Federal Circuit has noted, "[c]ombining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability--the essence of hindsight. *See, e.g., Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1138, 227 USPQ 543, 547 (Fed. Cir. 1985) ("The invention must be viewed not with the blueprint drawn by the inventor, but in the state of the art that existed at the time."). *In re Dembiczak*, No. 98-1498 (Fed. Cir., April 28, 1999). Applicants maintained in their last Amendment that the previous Action had failed to show that there was any motivation to combine the references as the Action had, absent the teachings of the specification.

The present Action responds by asserting that a motivation to combine the references is in fact present. At page 16, the Action cites a line in Phillip, at page 3137, that "the goal of this study was to elucidate the genomic organization of *M. tuberculosis* and to establish a set of ordered DNA fragments, a valuable genetic resource." This is of course true, but has little obvious relevance to providing motivation to make primer pairs which specifically amplify EtaA, as recited in the claims under examination. Elucidating the genomic organization, and

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establishing a set of ordered DNA fragments provides no apparent reason to create primers specific for any of the particular genes in the Mtb genome, let alone the EtaA gene.

The Action quotes Phillip as further teaching that "several recent examples leading to the identification of genes involved in drug resistance or encoding new therapeutic targets testify to the power of this approach." This statement, however, is taken out of context and has nothing to do with amplification of DNA sequences, let alone the amplification of EtaA, in particular. The sentence preceding the one quoted by the Action states: "The clones based on the shuttle vector pYUB18 should facilitate the dissection of the pathogenicity of the tubercule bacillus, as they can be introduced into easily manipulated surrogate hosts, such as *Mycobacterium smegmatis*, where faithful gene expression can be obtained." [Philipp, at page 3137, left column. Emphasis added, citation omitted]. This sentence is then followed by the one quoted by the Action: "Several recent examples [citations omitted] leading to the identification of new genes involved in drug resistance or encoding new therapeutic targets testify to the power of this approach." Id. The "approach" referred to by Philipp, therefore, is the introduction of clones into surrogate hosts and the observation of the phenotype of the resulting organisms. The comments in Philipp therefore do not pertain to the amplification of ordered DNA fragments in general or to primers specific for amplifying the EtaA gene in particular, and would not lead the person of skill to combine the teachings of Philipp with references pertaining to PCR. Philipp therefore does not provide the motivation relied on by the Action for combining the references.

Finally, the Action asserts that "the reference [Philipp] teaches the use of PCR amplification using primers specific to the *Mycobacterium tuberculosis* sequence of genomic DNA in order to facilitate gene mapping, data handling and analysis (Pg. 3133). The examiner maintains that a motivation to combine the references thus exists." Action, at pages 16-17, bridging sentence.

Once again, the portion of Philipp quoted is taken out of context. What Philipp says, at the place cited, is:

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### Hybridization, Mapping, Data Handling and Analysis

To facilitate gene mapping and the construction of contigs by hybridization mapping [citation omitted], arrays of cosmids were dot blotted onto Hybond N membranes and processed as recommended by Amersham, Plc. The probes were macrorestriction fragments isolated from pulsed-field gels and labeled in the gel slice, whole cosmids, repetitive sequences, or single-copy probes produced either from cloned genes or by PCR amplification of genomic DNA [citation omitted].

The Action asserts that this passage provides motivation to combine the references. But what the passage says is no more than that the gene mapping and data handling were facilitated by immobilizing cosmids on membranes and probing the membranes with probes, which could be single-copy probes produced from cloned genes or by PCR amplification of genomic DNA. There is no indication that any particular portion of genomic DNA or that any particular gene would be any more useful than any other for probing immobilized cosmids on a membrane. Certainly, the motivation to combine the references allegedly present in the passage is not explained by the Action, which merely states a conclusion without presenting any reasoning or analysis to support it.

The Action provides no analysis or reasoning why the practitioner would take the general disclosure of Philipp about probing cosmids with amplified genomic DNA and combine it with Badcock's unpublished disclosure of a probable monooxygenase encoded by 1400 nucleotides of a reported 38,000 nucleotide sequence to render obvious kits with primers specific for that 1400 nucleotides. The Action merely states it as a conclusion, and leaves it to the reader to deduce the reasons that might provide such a motivation.

An unsupported conclusion, however, does not meet the Office's burden to show the logic for a combination. As Applicants pointed out in their last Amendment, the Federal Circuit requires that the examiner: "show reasons that the skilled artisan, confronted with the same problems as the inventor and no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner cited." *In re Rouffet*, 47 USPQ2d 1453 (1998) (Emphasis added.)

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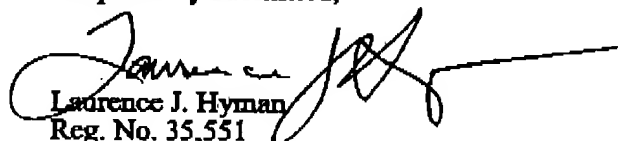
The present Action, like the previous Action, fails to show "reasons that the skilled artisan, confronted with the same problems as the inventor and no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner cited," as required by *Rouffet*. In the absence of such a showing, the conclusion is once again warranted that the Action has simply picked and chosen from the art to recreate the invention. Applicants therefore respectfully submit that the Action has once again failed to present a proper *prima facie* case of obviousness. The rejection should be reconsidered and, upon reconsideration, withdrawn.

**CONCLUSION**

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

  
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